Maggie's Mysterious Hiccups

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Introduction:

Hypoadrenocorticism (HOAC), or Addison's disease, is an endocrine condition in which adrenal hormone secretion is impaired or below the physiologic requirement of the animal.[1] These patients can present in a variety of ways from nonspecific waxing and waning gastrointestinal upset to acute hypovolemic shock and collapse. In the most common presentation of the disease, HOAC results in both mineralocorticoid and glucocorticoid deficiency (i.e. mineralocorticoid and glucocorticoid deficient hypoadrenocorticism; MGDH) and animals experience electrolyte abnormalities including hyponatremia and hyperkalemia, as well as signs of cortisol deficiency.[2] This is not always the case, however, and in some instances only cortisol deficiency can be confirmed, a condition called glucocorticoid-deficient hypoadrenocorticism (GDH) or Atypical Addison's disease.[3] GDH describes an animal with adrenal glands that still produce mineralocorticoids but lack sufficient glucocorticoid production. While GDH is still considered to be a very rare endocrinopathy, within the past ten years it has started to be reported with increasing numbers and is now identified in up to 30-40% of dogs diagnosed with HOAC.[3] This is presumed not to be an indication of increased prevalence, but to be representative of increased awareness of GDH as well as the routine performance of ACTH-stimulation tests on dogs with nonspecific gastrointestinal signs.

Patients with GDH often are diagnosed further along in the disease process compared to those with mineralocorticoid deficiency due to more subtle clinopathologic changes and less severe clinical signs that can be overlooked by clinicians. On CBC/chem often there is absence of a stress leukogram, anemia, eosinophilia and/or hypoglycemia, although patients may present with no bloodwork abnormalities at all. Additionally, due to sufficient mineralocorticoid production, patients will not present with the classic electrolyte abnormalities that are commonly

used to point in the direction of Addison's disease. Clinical signs of GDH varies from one individual to another and usually develops slowly over time. Most frequently reported clinical signs include non-specific gastrointestinal signs such as vomiting, diarrhea, melena, and weight loss. Hypovolemic shock is also an unlikely sequala of glucocorticoid deficiency but very rarely can occur with severe gastrointestinal hemorrhage.[4]

Through an examination of current literature and past reports, this case report outlines a rare case of GDH where the patient presented with clinical signs currently unestablished within veterinary medicine. This paper will also outline the clinical signs, diagnostic strategy, prognosis, pathophysiology, and treatment options for glucocorticoid-deficient hypoadrenocorticism to further establish accurate identification and treatment of the disease.

History and Presentation:

Maggie is a 5-year-old female spayed Labrador Retriever that presented to the MSU-CVM Internal Medicine service on 12/30/21 for episodic bloating over the period of 2 weeks. On 12/16/21, Maggie had her first episode of what her owner described as "hiccups". The episode lasted for approximately 45 minutes, and she then proceeded to vomit 4-5 times during the incident. The episode was not related to her eating or drinking, although there was inconsistent history of her seeming dysphagic to her owners. The following day, radiographs were performed, and the clinician noted suspicion for a gastric mass. Maggie was prescribed sucralfate and omeprazole with no improvement. She continued to have episodes of "hiccups" with no further associated vomiting. Maggie's owner then sought a second opinion on 12/18/21 where radiographs were rechecked, and no gastric mass was noted. At this time bloodwork was also

performed which showed eosinophilia. Maggie was then prescribed an unknown dewormer, metronidazole and Clavamox. Unclear if she had been experiencing dysphagia, her owners began slow feedings at home. Despite medical and environmental therapy, her owner reported that the episodes started to occur with increased frequency and lasted for longer periods of time with most episodes lasting longer than one hour. It was on 12/29/21 that Maggie had an episode that lasted approximately 3 hours and she began to have diarrhea, which prompted her owners to bring her in to Mississippi State University College of Veterinary Medicine (MSU-CVM), Internal Medicine service. Otherwise, Maggie continued to appear bright and alert with no changes in appetite, drinking, or urination.

Upon presentation, Maggie was bright, anxious, and responsive. She weighed 22.7 kgs and had a body condition score of 8/9 (with 4-5/9 being ideal). Maggie's vitals were as follows; her heart rate was 120 beats per minute, her rectal temperature was slightly elevated at 103.5*F, and she was panting. On cardiopulmonary auscultation, no crackles, wheezes, murmurs, or arrhythmias were appreciated. Her mucous membranes were pink and moist with a capillary refill time of less than 2 seconds. Her femoral pulses were strong and synchronous. Her peripheral lymph nodes were mildly enlarged and firm. A rectal exam was performed revealing normal feces with no other significant findings. Maggie's abdomen palpated tense but non-painful and no free fluid was appreciated on AFAST or TFAST. Maggie was observed eating and drinking with no discernable dysphagia appreciated.

Diagnostic Approach and Differential Diagnoses:

As in most cases of glucocorticoid-deficient hypoadrenocorticism (GDH), Maggie presented with non-specific gastrointestinal signs including episodic bloating, and one episode of

vomiting and diarrhea. From that information alone, her list of differentials diagnoses included pretty much anything that could cause gastrointestinal upset including food sensitive gastritis or food-responsive enteropathy, pancreatitis, parasitism, IBD, obstruction, and hypoadrenocorticism.

Initially, a CBC and chemistry were unremarkable with only a mild neutrophilia and no evidence of a stress leukogram. Maggie had abdominal radiographs performed which revealed soft tissue opaque material within the stomach and pylorus; differentials include normal ingesta vs non-obstructive foreign material. While Maggie's peripheral lymph nodes were only mildly enlarged, aspirates were performed for complete evaluation and surprisingly cytology was diagnostic of eosinophilic lymphadenitis.

Eosinophilia and eosinophilic lymphadenitis most commonly occur as a leukemoid response or when eosinophil counts increase to high levels in response to an underlying cause. Differentials include parasitic etiologies including Dirofilaria immitis, hypersensitivities such as flea allergy dermatitis and food allergies, eosinophilic infiltrative disorders, infectious diseases including certain chronic upper respiratory disease, pneumonia, metritis, mastitis, and lower urinary tract infection, neoplastic processes, eosinophilic inflammatory bowel disease, and less commonly endocrinopathies such as hypoadrenocorticism.[5]

A fecal smear was performed which did not reveal ova/parasites. A 4DX was ran which was nondiagnostic for heartworm, Anaplasma, Ehrlichia, and Lyme disease. An abdominal ultrasound was then performed; most significant findings including the left adrenal gland measuring 0.35 cm in diameter, which is at the lower end of the reference interval, a subjectively small liver with a hyperechoic structure within the left subsegment, differentials including cirrhosis, fibrosis, microvascular dysplasia, or portosystemic shunt- although no

anomalous vessels were identified in the study, and a mildly enlarged right iliac lymph node differentials being normal finding vs. reactive lymph node. No evidence of a gastric mass or foreign body were appreciated on ultrasound. Due her inconsistent history of dysphagia, a swallow study was performed for thorough evaluation which revealed no significant abnormalities and Maggie continued to display no signs of dysphagia while in hospital.

Finally, causes of chronic and persistent hiccups are rarely documented in veterinary medicine, although gastric issues such as vomiting and diarrhea, presence of parasites, respiratory issues, and endocrine disorders have been associated with abnormal hiccups in human patients. Anecdotally, hiccups have been thought to be caused potentially by esophagitis or gastroesophageal reflux. Hiccups are a form of myoclonus, or quick involuntary muscle spasms. Similar muscle disorders have been documented in dogs with hypoadrenocorticism in which dogs a week prior to diagnosis presented with myotonia, or painful muscle cramps.[6] This information led us to consider hypoadrenocorticism as a differential diagnosis as well.

Due to Maggie's history of intermittent gastrointestinal signs and eosinophilia, along with ultrasound findings of the left adrenal gland measuring at the lower end of the reference interval, suspicion was raised for glucocorticoid-deficient hypoadrenocorticism (GDH). Diagnosis of GDH is based on decreased (<2 ug/dl) resting cortisol levels without a significant increase after ACTH administration (post <2 ug/dl).[4] Maggie's baseline cortisol was <1 ug/dl; she was then administered a 0.25 mg/kg dose of Cosyntropin (Cortrosyn) intravenously and cortisol was evaluated again one hour post administration. Her post cortisol was <1 ug/dl and she was confirmed to have glucocorticoid deficient hypoadrenocorticism.

To exclude the possibility of secondary hypoadrenocorticism, ACTH concentration may be assessed. In dogs with primary hypoadrenocorticism, ACTH concentration is expected to be

increased over the reference range, with the normal range being 10-80 pg/ml.[7] Maggie's endogenous ACTH returned as 483 pg/ml and she was determined to have primary GDH.

It is also recommended to perform aldosterone levels, as it has been shown that some dogs with combined glucocorticoid and mineralocorticoid deficiency present with sodium and potassium concentrations within the normal range and as such electrolyte concentrations are not sufficient to make a diagnosis of isolated GDH.[1,7] Maggie's Aldosterone was within normal range (62 pmol/L, reference range 14-957 pmol/L) and as such, she was confirmed to have isolated GDH.

Pathophysiology:

In general, hypoadrenocorticism is most commonly a result of immune-mediated destruction of the adrenal cortex, also referred to as primary hypoadrenocortism (HOAC). This results in the inability of the synthesis and secretion of cortisol as well as aldosterone. Less commonly, primary hypoadrenocorticism can be iatrogenic due to mitotane, trilostane, or chronic steroid usage, due to a neoplastic process, or caused by granulomatous disease.[2,4,8] Animals can also have a pituitary gland lesion which would result in depletion of ACTH and would primarily affect cortisol production, referred to as secondary HOAC. As discussed earlier, glucocorticoid deficient hypoadrenocorticism can be primary or secondary and this can be determined by running an endogenous ACTH, as you would expect levels to be well above the reference range with primary GDH.[4,8]

As a review of normal physiology, the adrenal glands consists of two distinct parts, the outer cortex and inner medulla. The adrenal cortex is then divided into three distinct layers or zones. From outermost to innermost, the zona glomerulosa is responsible for the production and

secretion of mineralocorticoids, the zona fasciculata is responsible for the production of glucocorticoids and to a lesser extent produces sex steroids, and the zona reticularis is responsible for the secretion of sex steroids.[4,5] Aldosterone and cortisol are the primary mineralocorticoids and glucocorticoids produced in the canine, respectively.[4] The renin-angiotensin system plays an important role in stimulation of aldosterone secretion with a small role of ACTH during severe volume depletion. Aldosterone primarily results in reabsorption of sodium and chloride and the secretion of potassium and hydrogen ions, and when deficient can result in severe and sometimes fatal hyperkalemia and hyponatremia, characteristic of Addison's disease.[8,9,10] Cortisol however is primarily regulated by the hypothalamic-pituitary-adrenal (HPA) axis with ACTH stimulating production. Cortisol plays an important role in suppressing inflammatory and immunologic responses, results in the sparing of glucose, and tends to cause hyperglycemia and an increase in glucose production.[9,10]

It is important to make the distinction between the clinical signs caused from aldosterone verses cortisol deficiency. In the classic presentation of Addison's disease, both deficiencies will be present. As a result of aldosterone deficiency, the animal may be severely volume depleted with a various combination of electrolyte abnormalities, including hyperkalemia, hyponatremia, hypochloridemia, and hypercalcemia.[4] Hyponatremia and hyperkalemia causes the "hallmark of Addison's disease" which is a low sodium to potassium ratio of less than 25-27.[4,11] Hyperkalemia can produce ECG abnormalities including a spiked T wave, decreased P, R wave amplitudes, increased P, P-R, and QRS durations, loss of P wave, and marked bradycardia with heart block, severe arrhythmias, and even cardiac arrest.[8] Aldosterone deficiency is also primarily responsible for the polyuria and polydipsia which can be seen. Microcardia is documented on occasion and is primarily associated with volume disturbance with aldosterone

deficiency. In contrast, cortisol is responsible for gastrointestinal signs including vomiting and diarrhea, can cause hypoglycemia, and can result in the lack of maintenance of vascular tone.[2,8] Other diagnostic abnormalities can include megaesophagus, which is associated with lack of efficient glycogen storage and eventual loss of tone. With both deficiencies you can see lethargy/weakness, collapse, and hypovolemic shock, although animals with GDH are less likely to develop shock.[3]

One interesting anomaly of Maggie's presenting clinical signs is that she experienced chronic and persistent hiccups for hours at a time. In veterinary medicine, hiccups have rarely been documented as a presenting clinical sign. By definition, a hiccup is an intermittent spasmodic contraction of the diaphragm that can be central or peripheral in origin. Peripherally, any irritation to the phrenic, vagus, or upper spinal nerve, or centrally, excitation to the motor cortex, can cause hiccups.[5,12] There have been few reports in human medicine of early, very disturbing, and exhausting hiccups being a notable clinical sign of Addison's disease that were cured with steroid replacement; however no such documentation exists in veterinary medicine at this time.[12] One explanation that has been postulated is that hiccups and vomiting in Addison's disease can be explained by phrenic and vagus nerve irritation or hypersensitivity. Another theory is that since Addisonian patients frequently have abnormal electroencephalogram (EEG) readings, that a central cause of hiccups can not be ruled out.[12]

Treatment:

Treatment of glucocorticoid deficient hypoadrenocorticism involves lifelong cortisol supplementation. In acute situations, Dexamethasone- SP may be used at a dose of 0.05-0.14 mg/kg (typically a 1mg/kg prednisone dose equivalent) intravenously, as this is the only

treatment option that can be administered without affecting the cortisol assay used for the ACTH stimulation test. Once stabilized, the patient can be transitioned to oral prednisone at 0.2-0.4 mg/kg once per day. At follow up checks, the prednisone dose should be adjusted based on clinical signs so that the patient is on the lowest dose that will maintain a good quality of life.[4] Owners should be cautioned that dogs will often need a dose increase during stressful situations such as vacations, trips to the vet, boarding, or any other event that may cause stress. In these situations, owners should be instructed to administer prednisone at 0.5-1 mg/kg throughout the stressful event and then tapered to lowest effective dose.[7,10]

Unlike the classic presentation of Addison's disease, mineralocorticoid supplementation is not necessary with GDH. However, it very important to note that most dogs with GDH eventually develop electrolyte abnormalities. Therefore, it is important to ensure frequent initial electrolyte checks to ensure the patient is not progressing to have mineralocorticoid deficiency as well. Therefore, it should be discussed with owners that electrolytes should be checked at 1, 3, and 6 months following diagnosis, and every 6 months thereafter to ensure that the animal does not need mineralocorticoid supplementation through monthly Desoxycorticosterone Pivalate (DOCP) injections or daily oral fludrocortisone administration.[7,8]

Maggie was discharged with 0.45 mg/kg prednisone once daily for 14 days in addition to maropitant citrate at 2.6 mg/kg once daily for 7 days for nausea and vomiting, and metoclopramide 0.45 mg/kg every 8 hours for 7 days as an antiemetic and motility stimulator. Her owner was instructed to make an appointment with MSU-CVM in 2 weeks where a chemistry panel would be performed to evaluate electrolytes and to possibly decrease prednisone dose depending on clinical signs.

Discussion:

Given patients that have committed caregivers, the long-term prognosis for dogs with GDH is generally excellent. With proper glucocorticoid supplementation through daily prednisone administration, these dogs can live normal and comfortable lives. Owners do need to be made aware that while hypovolemic shock is less likely in patients with GDH, it is still possible. It is important that owners are mindful of clinical signs to look out for such as extreme exhaustion, severe weakness, pale gums, and/or cold ears/extremities and be directed that if any of these signs develop to seek emergency veterinary care immediately.[11] Owners should also be well informed that many dogs with GDH develop a mineralocorticoid deficit in the following weeks, months, to years and that they need to be prudent to take their pet to the vet for recheck electrolyte screens at 1, 3, and 6 months following diagnosis, and every 6 months thereafter.[7,8,11]

Following Maggie's diagnosis and treatment with corticosteroids, she has had no further episodes of hiccups, bloating, vomiting, or diarrhea. Her mom reports that she is doing excellent at home; she has so much more energy and now runs around like normal with her siblings. As of March of 2022, Maggie has returned electrolytes within normal range and has not required any mineralocorticoid treatment, although her owner has been instructed to continue bringing her for rechecks every 6 months to monitor electrolytes for any changes.

Maggie's case is a great example of how subtle, non-specific, and varied clinical signs of GDH can be, and highlights how this can be an easily missed diagnosis. Again, the only significant findings that led to her diagnosis were her history of bloating, one episode of vomiting and diarrhea, her historical eosinophilia, and ultrasound findings documenting one adrenal gland to be on the lower end of the normal range. This highlights how important it is to perform ACTH stimulation tests in dogs with non-specific gastrointestinal signs, regardless of

the presence of electrolyte abnormalities especially if all other differentials have been ruled out. In addition, this case study found that hiccups may be associated with glucocorticoid deficient hypoadrenocorticism, although the exact mechanism is unclear. While hiccups may be a rare presenting clinical sign, this suggests that it is worthwhile to perform an ACTH-stimulation test to rule out hypoadrenocorticism when hiccups are persistent and chronic in nature.

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